some exposure to passive smoke, most often in places outside the home. Testing for urinary or salivary levels of cotinine, a by-product of cigarette smoke, has documented the presence of tobacco smoke exposure in a large proportion of the general population.

Secondhand smoke is now recognized as a health threat in this country. This has caused a dramatic change in public attitudes regarding the rights of the smoking minority versus the welfare of the nonsmoking public. Further research is needed to determine more precisely how great the risk is from this exposure.

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Immunoglobulin G Subclasses

THE FOUR IMMUNOGLOBULIN (Ig) G subclasses are products of discrete constant region genes encoded within the immunoglobulin heavy-chain locus on chromosome 14. Each immunoglobulin represents the expression of several rearranged variable region genes with one constant region gene producing a single polypeptide chain. The finished immunoglobulin molecule is a four-chain structure composed of two identical heavy chains coupled to two identical light chains (κ or λ) encoded on chromosomes 2 and 22, respectively. Monoclonal antibody and recombinant genetic technology have resulted in major advances in understanding immunoglobulin structure-function relationships as well as accurate methods for measuring IgG subclasses and specific antibodies to defined antigens.

Studies of purified isolates of human IgG subclasses, or genetically constructed antibodies of identical variable regions (idiotype) but different constant regions (isotype), have supplemented and clarified earlier studies of naturally occurring antibodies. These studies confirm major effector differences in IgG subclass antibodies. IgG3 is more efficient than IgG1 in activating complement, but IgG2 is minimally active and IgG4 is inactive. IgG1 is more efficient than IgG2 in enhancing human complement-mediated killing of some bacterial pathogens. IgG4 is functionally univalent and does not form large latticed immune complexes. Although these differences may have clinical implications, extrapolation from in vitro studies to defense capabilities in vivo may be misleading because of the physiologic redundancy of defense mechanisms.

Minor IgG subclass deficiencies have been linked to an increased susceptibility to infection. Often IgG2 or IgG2 to IgG4 deficiency occurs along with IgA deficiency. The strongest disease association has been that of low IgG2 levels and recurrent infection with encapsulated bacteria such as *Haemophilus influenzae* type b and *Streptococcus pneumoniae*. The clinical implications of low IgG subclass levels are not well understood, however. Healthy persons lacking constant region genes for one or more IgG subclasses have been identified; healthy blood donors with variable IgG subclass deficiencies have also been found; persons with initially low IgG subclass levels can correct over time; and, finally, normal IgG subclass levels but deficient specific antibody responses have been described in persons with recurrent infection. Thus, IgG subclass deficiencies are likely markers of broader immune abnormalities rather than inherent causes of disease. The best understood example of this is also IgG2 deficiency. Low IgG2 levels in patients with recurrent infection are associated with an inability to respond to bacterial polysaccharides, but in healthy IgG2-deficient persons, normal antibody responses are seen. This suggests that the primary defect is specific immune responsiveness to bacterial polysaccharides; if impaired, low IgG2 levels are frequently but not invariably found. Therefore, the assessment of recurrent sinopulmonary or systemic pyogenic infection—the major indication for evaluating IgG subclasses—should include both IgG subclass levels and specific antibody responses to protein and polysaccharide antigens, including the paired measurement of serum before and four weeks after immunization with capsular vaccines such as unconjugated *H influenzae* type b and pneumococcal polysaccharide vaccine. Age-related interpretation is essential because healthy infants and toddlers may not respond to these vaccines. At present, IgG subclass-specific antibody assays are not generally available. An IgG subclass deficiency associated with impaired antibody responses can be treated with intravenous immune globulin if conservative measures such as antibiotic prophylaxis are ineffective. The use of intravenous immune globulin therapy in patients with an IgG subclass deficiency without a demonstrably impaired antibody response is controversial; many clinicians await the results of a multicenter controlled trial now in progress.

An analysis of IgG subclass levels must take into account their non-Gaussian distribution, wide normal ranges, and ethnic differences. Allelic population differences in certain heavy- and light-chain regions (allotypes) can affect IgG subclass levels and specific antibody responses. For example, whites with the IgG2m(n) allotype have higher IgG2 levels and antibody responses to bacterial polysaccharides than persons lacking this allele. Adult levels of IgG1 and IgG3 are attained earlier than levels of IgG2 and IgG4. For IgG3 and especially for IgG4, true deficiencies are hard to establish, given that low levels are found in many normal younger children.

Generally, antibody responses to protein antigens—such as viral envelopes—mainly involve IgG1 and IgG3. Antibody responses to capsular polysaccharides seem to fall into two groups, those eliciting greater IgG2 isotype restriction such as *S pneumoniae* and those with a lesser degree of IgG2 restriction such as *H influenzae* or meningococcal types A and C, where substantial IgG1 responses may occur. Finally, antibody responses to protein antigens presented repetitively, such as allergen extracts used in hyposensitization therapy, are largely restricted to IgG1 and IgG4, with the latter often predominant.

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